AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the applications.

Listing of Claims:

Claims 1-103 (canceled)

104. (currently amended) The method of claim [[102]] 110, wherein the peptide comprises a sequence of amino acids defined by the formula P_2P_1-P_1'P_2P_3', wherein

~~P_2 comprises an amino acid selected from the group consisting of N, S, and D;~~

~~P_1 comprises an amino acid selected from the group consisting of Y, F and L;~~

~~P_1' comprises an amino acid selected from the group consisting of E, A, and D;~~

~~P_2' comprises an amino acid selected from the group consisting of A and V;~~

P_3' comprises an amino acid selected from the group consisting of E, G, F, H, cysteic acid and S.

105. (currently amended) The method of claim [[102]] 110, wherein the peptide comprises a sequence of amino acids defined by the formula P_2P_1-P_1'P_2P_3', wherein

~~P_2 comprises an amino acid selected from the group consisting of S, N, F, and K;~~

~~P_1 comprises an amino acid selected from the group consisting of F, L, Y, and M;~~

~~P_1' comprises an amino acid selected from the group consisting of E, D, and A;~~

~~P_2' comprises an amino acid selected from the group consisting of A and V;~~

P_3' is E.

106. (currently amended) The method of claim [[102]] 104, wherein the peptide comprises a sequence of amino acids defined by the formula $P_3P_2P_1$-$P_1'P_2'P_3'$, wherein P_3 is an amino acid selected from the group consisting of A, V, I, S, H, Y, T and F.

107. (previously presented) The method of claim 106, wherein P_3 comprises an amino acid selected from the group consisting of I or V.

108. (previously presented) The method of claim 106, wherein the peptide comprises a sequence of amino acids defined by the formula $P_4P_3P_2P_1$-$P_1'P_2'P_3'$ wherein P_4 is an amino acid selected from the group consisting of E, G, I, D, T, cysteic acid and S.

109. (previously presented) The method of claim 108, wherein the peptide comprises a sequence of amino acids defined by the formula $P_4P_3P_2P_1$-$P_1'P_2'P_3'P_4'$, wherein P_4' is an amino acid selected from the group consisting of F, W, G, A, H, P, G, N, S, and E.

110. (currently amended) ~~The~~ A method for assaying for modulators of β-secretase activity, comprising:

(a) contacting a polypeptide with β-secretase APP processing activity with a substrate, both in the presence and in the absence of a putative modulator compound;

wherein said substrate comprises a peptide having an amino acid sequence of at least 6 amino acids, said amino acid sequence including four amino acids defined by formula P_2P_1-$P_1'P_2'$, ~~of claim 102~~, wherein the amino acids at positions P_2, P_1, P_1', P_2' comprise S, Y, E and V, respectively,

(b) measuring cleavage of the substrate peptide in the presence and in the absence of the putative modulator compound; and

(c) identifying modulators of β-secretase activity from a difference in substrate cleavage in the presence versus in the absence of the putative modulator compound, wherein a modulator that is a β-secretase antagonist reduces such cleavage and a modulator that is a β- secretase agonist increases such cleavage.

111. (previously presented) The method of claim 110, wherein said peptide comprises the amino acid sequence SEISY-EVEFR (SEQ ID NO: 152).

112. (previously presented) The method of claim 110, wherein said peptide comprises the amino acid sequence SEISY-EVEFRWKK (SEQ ID NO: 190).

113. (previously presented) The method of claim 110, wherein said peptide comprises the amino acid sequence GLTNIKTEEISEISY-EVEFRWKK (SEQ ID NO: 191).

114. (currently amended) The method of claim 110, wherein said peptide comprises the amino acid sequence SEVSY-EVEFR (SEQ ID NO: 141).

115. (previously presented) The method of claim 110, wherein said peptide comprises the amino acid sequence KTEEISEVSY-EVEFR (SEQ ID NO: 147).

116. (previously presented) The method of claim 115, wherein said peptide comprises the amino acid sequence TRPGSGLTNIKTEEISEVSY-EVEFR (SEQ ID NO: 145).

117. (canceled)

118. (currently amended) The method of claim [[102]] 110, wherein said substrate comprises an amyloid precursor protein (APP) amino acid sequence with a modified β-secretase processing site defined by said formula P_2P_1-$P_1'P_2'$.

119. (currently amended) The method of any one of claims ~~102-117~~ 110-116 or 118, wherein said peptide comprises an amino acid sequence having up to 50 amino acids.

120. (currently amended) The method of any one of claims ~~102-118~~ 110-116 or 118 wherein the peptide further comprises a first label.

121. (previously presented) The method of claim 120 wherein the peptide further comprises a second label.

122. (currently amended) The method of any one of claims ~~102-117~~ 110-116 or 118 wherein the peptide further comprises a detectable label and a quenching moiety, wherein cleavage of the peptide between P_1 and P_1· separates the quenching moiety from the label to permit detection of the label.

123. (currently amended) The method of claim ~~103 or~~ 108, wherein said cysteic acid comprises a covalently attached label.

124. (currently amended) The method of any one of claims ~~102-118~~ 110-116 or 118, wherein the rate of cleavage of said peptide by said human aspartyl protease is greater than the rate of cleavage of a polypeptide comprising the human APP β-secretase cleavage sequence: SEVKMDAEFR (SEQ ID NO: 20).

125. (currently amended) The method of any one of claims ~~102-118~~ 110-116 or 118, wherein the rate of cleavage of said peptide by said human aspartyl protease is greater than the rate of cleavage of a polypeptide comprising the human APP Swedish KM→NL mutation, β-secretase cleavage sequence SEVNLDAEFR (SEQ ID NO: 19).

126. (currently amended) The method of any one of claims ~~102-118~~ 110-116 or 118, wherein the polypepetide with β-secretase APP processing activity comprises an amino acid sequence selected from the group consisting of

(a) the amino acid sequence of SEQ ID NO: 2,

(b) a fragment of the amino acid sequence of SEQ ID NO: 2 that retains β-secretase APP processing activity, wherein said fragment includes the aspartyl protease active site tripeptides DTG and DSG,

(c) an amino acid sequence that is at least 95% identical to (a) or (b), wherein the polypeptide includes the aspartyl protease active site tripeptides DTG and DSG and exhibits β-secretase APP processing activity;

(d) the amino acid sequence SEQ ID NO: 4,

(e) a fragment of the amino acid sequence of SEQ ID NO: 4 that retains β-secretase APP processing activity, wherein said fragment includes the aspartyl protease active site tripeptides DTG and DSG, and

(f) an amino acid sequence that is at least 95% identical to (d) or (e), wherein said fragment includes the aspartyl protease active site tripeptides DTG and DSG and exhibits β-secretase APP processing activity.

127. (currently amended) The method of any one of claims ~~102-118~~ 110-116 or 118, wherein the polypeptide with β-secretase APP processing activity comprises an amino acid sequence selected from the group consisting of

(a) the amino acid sequence of SEQ ID NO: 2; and

(b) a fragment of the amino acid sequence of SEQ ID NO: 2 that retains β-secretase APP processing activity, wherein said fragment includes the aspartyl protease active site tripeptides DTG and DSG.

128. (previously presented)A method according to claim 126, wherein the polypeptide with β-secretase APP processing activity comprises a polypeptide purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide.

129. (previously presented) A method according to claim 118,

wherein the substrate is expressed in a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the substrate,

wherein the cell expresses the polypeptide with β-secretase APP processing activity;

wherein the contacting comprises growing the cell in the presence and absence of the test agent, and

wherein the measuring step comprises measuring APP processing activity of the cell.

130. (previously presented) A method according to claim 129, wherein the contacting comprises administering the test agent to a transgenic non-human mammal that comprises the cell.

131. (currently amended) A method according to claim [[102]] 110, wherein the polypeptide is encoded by a polynucleotide comprising the nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO; 3,

(b) a nucleotide sequence that hybridizes under the following stringent hybridization conditions to the complement of SEQ ID NO: 1 or 3:

(1) hybridization at 42°C in a hybridization buffer comprising 6x SSC and 0.1% SDS, and

(2) washing at 65°C in a wash solution comprising 1x SSC and 0.1% SDS;

wherein said nucleotide sequence encodes a polypeptide that exhibits β-secretase APP processing activity.